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**Simulation or Cohort Models?  
Continuous Time Simulation and  
Discretized Markov Models to  
Estimate Cost-Effectiveness**

**CHE Research Paper 56**



# **Simulation or cohort models? Continuous time simulation and discretized Markov models to estimate cost-effectiveness**

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## **Abstract**

The choice of model design for decision analytic models in cost-effectiveness analysis has been the subject of discussion. The current work addresses this issue by noting that, when time is to be explicitly modelled, we need to represent phenomena occurring in continuous time. Multistate models evaluated in continuous time might be used but closed form solutions of expected time in each state may not exist or may be difficult to obtain. Two approximations can then be used for cost-effectiveness estimation: (1) simulation models, where continuous time estimates are obtained through Monte Carlo simulation, and (2) discretized models. This work draws recommendations on their use by showing that, when these alternative models can be applied, it is preferable to implement a cohort discretized model than a simulation model. Whilst the bias from the first can be minimized by reducing the cycle length, the second is inherently stochastic. Even though specialized literature advocates this framework, the current practice in economic evaluation is to define clinically meaningful cycle lengths for discretized models, disregarding potential biases.



## 1. Introduction

Decisions to fund and use health care technologies are increasingly informed by cost-effectiveness analysis (CEA). The goal of CEA is to identify the 'preferred' option from a choice of health technologies to fund from available resources. This goal is achieved through measurement of the expected marginal costs and effects associated with the displacement of a health technology by a new one.<sup>1</sup> The outcomes of the analysis are the incremental cost-effectiveness ratio (ICER) — the additional cost per extra unit of effect from the more effective option<sup>2</sup> — or the net benefit (NB) statistic. To make a decision regarding which treatment option is cost effective, a decision rule is then applied.<sup>3</sup> Given that there is uncertainty in the joint distribution of incremental costs and effects, the decision itself is uncertain. An assessment of this uncertainty is a key requirement of economic evaluation for decision making<sup>4</sup> and can be used to establish the value of further research.<sup>5</sup>

Agencies such as the UK National Institute for Health and Clinical Excellence (NICE) require that all relevant available evidence should be considered to inform decision making. In the presence of multiple sources of information, this involves bringing together and synthesising evidence appropriately in terms of input data, e.g. mortality, relative risks or utility weights.<sup>6,7</sup> Based on these input parameters, the expected cost and effect is calculated for each alternative treatment option by weighting the likelihood of disease consequences by their cost. The mathematical relations between inputs from different sources and outputs are brought together by a decision analytic model (DAM).

The design and structure of DAMs should characterise the consequences of alternative treatment options in a way that is appropriate to the decision problem. DAMs can be based on cohort (aggregated) models. These are defined here as having a closed form solution, that is the expected costs and effects based on the average patient experience are evaluated algebraically, although there are other definitions. The majority of DAMs applied in the context of chronic or long-term diseases use aggregated state transition models<sup>8</sup>, and assume independence of individuals within the model.<sup>9</sup> These models are defined by a set of mutually exclusive health states and the movement between these states through time represents possible patient disease (or health) pathways to which costs and effects can be assigned. When discrete time models, such as discrete time Markov models<sup>10,11</sup>, are defined, the probability of occupying a given state is assessed over a series of discrete and constant time periods, known as cycles. An important characteristic of Markov models is that future development of the process is not dependent on the history of the process, just on the present (Markov property). Although this property can simplify the use of such models, it is often unrealistic. To circumvent dependency on time spent in a specific state a set of tunnel states can be implemented in a Markov framework<sup>10</sup> or a semi-Markov framework<sup>12,13</sup> may be used.

However, it is important to note that time has a continuous nature. When the decision problem relates to a chronic disease, the phenomena one wishes to evaluate can be described as a series of events occurring through time; thus the theoretical model used to mimic such phenomena should ideally represent time as a continuous measure. Whilst continuous time models can be employed, they rarely are in practice since closed form solutions for the expected time spent in states may not exist when a continuous time formulation of a state transition model is used, such as for semi-Markov models.<sup>14</sup> Furthermore, even when such closed form solutions do exist, these can be mathematically demanding if, for example, the transition rates are not constant through time.<sup>15,16</sup> To overcome this issue a discrete time approximation (discretized cohort models) is often applied to continuous time phenomena. Whilst in continuous time models individuals can transit at any time to the absorbing state, in discretized models individuals can only transit in discrete time periods. An important issue when using discretization, or any numerical method, is that the shorter the discretization step (or cycle length) the better the approximation to continuous time model outcomes.<sup>17</sup> Although discrete time models are frequently applied in the evaluation of cost-effectiveness, the outcomes of such models are seldom regarded as approximations (to continuous time). As a result determinants of bias such as the cycle length are disregarded.

An alternative approach to the use of discretized cohort models to approximate continuous time phenomena is to estimate the continuous time process using Monte Carlo sampling; that is, applying a stochastic simulation model.<sup>18</sup> A stochastic algorithm is designed to simulate individual pathways, patient by patient.



Whichever DAM design is used, the parameters are uncertain since they are estimated directly from sampled data or from evidence synthesis procedures. The decision to adopt the new intervention will also be uncertain. It then matters to evaluate how confident we are that the intervention is cost-effective.<sup>19</sup> The propagation of the joint uncertainty on model inputs to model outputs is called probabilistic sensitivity analysis (PSA). This process is usually conducted by simulation: in a frequentist framework a second order Monte Carlo method is used, while in the Bayesian framework the uncertainty is represented directly by the posterior distribution of the ICER or NB.<sup>20,21</sup> PSA is relatively straightforward in cohort models. However, for individual stochastic simulation models the full assessment decision uncertainty using PSA may not be viable as two levels of simulation are required: for each realization of the set of uncertain parameters (as part of PSA), a Monte Carlo simulation is required to evaluate the expected values of outcomes.<sup>22</sup> Some authors disregard the use of these models when it compromises the evaluation of second order uncertainty.<sup>23</sup>

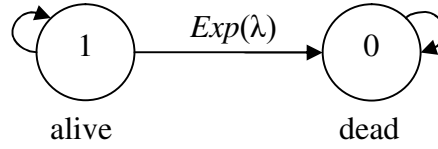
While the distinction between discrete time and continuous time is mathematically clear-cut, it is unclear from the existing literature how the use of a discrete time approximation to continuous time phenomena can affect the evaluation of cost-effectiveness, and hence the decision recommendation for the underlying policy problem. Alternatively, continuous time models evaluated by Monte Carlo simulation can be used to estimate the same outcomes. These return imprecise estimates and may place heavy demands upon computational resources, especially when a second simulation procedure for PSA is required. Although simulation and discrete model outcomes were previously compared<sup>24</sup>, the continuous nature of time was ignored and both models were built assuming discrete time. Additionally, published guidance on model design<sup>25</sup> does not explicitly consider discrete time models as approximations.

This work intends to draw recommendations on the use of discretized cohort model and simulation approaches, when these constitute alternative model designs in cost-effectiveness analysis aiming at evaluating a decision problem characterised by continuous time evolution. To pursue this in an intuitive way, a hypothetical decision problem will be defined where an exact solution for outcomes exists. This obliges the choice of a simple example, maybe unrepresentative of many DAMs as applied in current practice, but that demonstrates theoretical results obtainable with any other model.

The structure of the paper is as follows. In section 2, a hypothetical decision problem with known solutions for expected values of life time, incremental costs, incremental effects and cost-effectiveness will be set up. How to obtain approximations from discretized cohort Markov models and estimates from simulation models based on a continuous time Markov model is briefly described in section 2. Alongside, factors contributing to the precision and bias of the approximations will be identified. The comparison of Markov models estimates from a discretized model and a model evaluated by simulation is reported in section 3. Finally, the use of the referred alternative approximations to evaluate cost effectiveness is discussed (section 4).

## 2. Methods

In order to compare the cost-effectiveness estimates from stochastic simulation and cohort models, a true process representing reality is defined with two health states: alive and dead (Figure 1).



**Figure 1: Two state model including one absorbent state (dead state)**

An individual initiates the chain alive and may remain alive or die over time; that is, transit to state 0 (dead). Death is represented by an absorbent state from which there is zero probability of exiting. The transitions to death occur at a constant rate,  $\lambda$ . Consequently, time to event follows an exponential distribution,  $\text{Exp}(\lambda)$ .

### 2.1. Life expectancy

The above process can be perfectly described by a continuous time homogeneous Markov chain, where the probability of transiting between states is not dependent on time itself, but is dependent on the length of the time interval, or cycle, considered. For a continuous time two state process, the expected time until absorption, or life expectancy  $E[T]$ , can be defined as the expected value of the underlying distribution assumed for the time to transition. If the underlying distribution is exponential,  $E[T]$  is given by

$$E[T] = \frac{1}{\lambda} \quad (1)$$

where  $\lambda$  is the parameter of the exponential distribution.

Although approximations are unnecessary in the current example, the existence of the closed form solution of life expectancy allows evaluating bias associated with the estimates obtained through a discretized model and a continuous time simulation model.

#### **Discretized Markov models**

Numerical solutions, or quadrature methods, can be used to solve complex integrals and in the current context this involves evaluating the model in discrete time. In the Appendix, the general case for a discrete time homogeneous Markov model is detailed. The calculation of life expectancy is based on the probability of transiting in one cycle, which is naturally defined by the probability of a transition occurring in the same period of time in the corresponding continuous time process.<sup>26</sup> The

discretized transition probability of dying,  $P_{10}$ , for the two state model is  $1 - e^{-(H_T(t_{n+1}) - H_T(t_n))}$ , where  $H_T(t_n)$  represents the cumulative hazard function evaluated at time  $t_n$  for the random variable (r.v.)  $T$  representing time to death. When  $T$  assumes an exponential distribution the discretized one step transition probability can be simplified to

$$P_{10} = 1 - e^{-\lambda \cdot l} \quad (2)$$

where  $l$  is the cycle length. The unrestricted life expectancy, denoted here by  $E_1[T]$ , estimated by a two state discretized process can be defined by

$$E_1[T] = \frac{1}{P_{10}} \cdot l, \quad (3)$$

where the expected number of transitions until absorption is multiplied by the cycle length,  $l$ . The accuracy of using a discretized process to evaluate continuous time outcomes depends on the discretization of the continuous distribution into cycle lengths. As  $l$  tends to zero the discretized Markov chain converges to the continuous one.

CEA are conducted often assuming a finite time horizon,  $K$ , for outcome evaluation. A restricted life expectancy estimate,  $E_2[T]$ , for the model depicted in Figure 1 can be assessed through the unconditional probabilities (see Appendix 1), as given by:

$$E_2[T] = \sum_{n=0}^K P_{10}^n \cdot l, \quad (4)$$

### ***Continuous time Markov models evaluated through Monte Carlo simulation***

Monte Carlo methods rely on stochastic simulation, that is, in the reproduction of values from a probability distribution. A sample value of time until the occurrence of a discrete event (here death) is drawn from a predefined distribution. Costs and utilities are assigned to the time spent in the health state (here alive). The procedure is repeated  $N$  times and the sample average of the costs and benefits returns the best estimate for the expected costs and benefits associated with the intervention under evaluation. The estimates obtained with Monte Carlo simulation will be denoted by  $\hat{E}_3[T]$ . A detailed description of this procedure is shown in the Appendix. The validity of the Monte Carlo estimates is dependent on the evaluation of convergence and on the precision associated with the estimates. Precision relies on the size of the simulated sample.

## **2.2. Costs and QALYs**

Quality-adjusted life weights and unit costs are assigned to the time spent in states other than death. If unit costs and utility weights are assumed non-stochastic, i.e. have no uncertainty, it is possible to obtain a closed form solution for expected total costs and expected quality-adjusted life years (QALYs). The expected total costs,  $E[C]$ , and expected total QALYs,  $E[U]$ , are given by:

$$E[C] = E[T] \cdot c \quad \text{and} \quad E[U] = E[T] \cdot u \quad (5)$$

where  $c$  is the cost of being alive per unit of time and  $u$  is the utility weight of being alive. For simplicity,  $c$  and  $u$  are assumed constant over time and discounting procedures are not applied.

### 3. Discretized versus simulation Markov models. An evaluation of cost-effectiveness

The variable representing lifetime or time until absorption,  $T$ , is assumed to follow an exponential distribution with a rate parameter of  $\lambda$ . If  $\lambda = 0.1$  the expected time to absorption of a continuous time Markov chain (Equation 1) is given by the expected value of the exponential distribution, i.e. 10 time units (defined as years in this example).

#### 3.1. Estimates of life expectancy

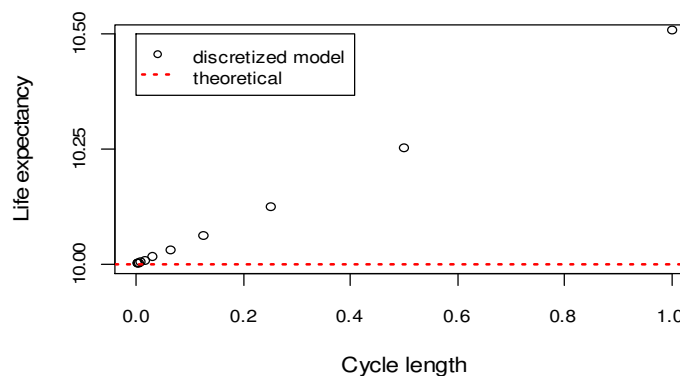
To evaluate the influence of the discretization step, unrestricted expected lifetimes (Equation 3) were obtained through the discretized homogeneous Markov model for different cycle lengths. In Table 1 and Figure 2 the life expectancy unrestricted estimates are reported for cycle lengths defined by  $\frac{1}{2^l}$

where  $l$  is an integer varying between 0 and 6. These estimates were obtained by evaluating a discrete time Markov process where the one step transition probabilities were estimated (Equation 2) as function of the theoretical continuous time rate and the cycle length. As an example, the transition probability between the states alive and dead assumes the value of 0.0952 for a cycle length of one year. The application of discretized models to assess continuous time phenomena will return approximate estimates, and the difference between the estimate or approximate value and the true value was assessed as an empirical measure of bias.

**Table 1: Discretized Markov model evaluations of life expectancy, conditional on cycle length. Estimates obtained from unrestricted and restricted solutions of the discretized process.**

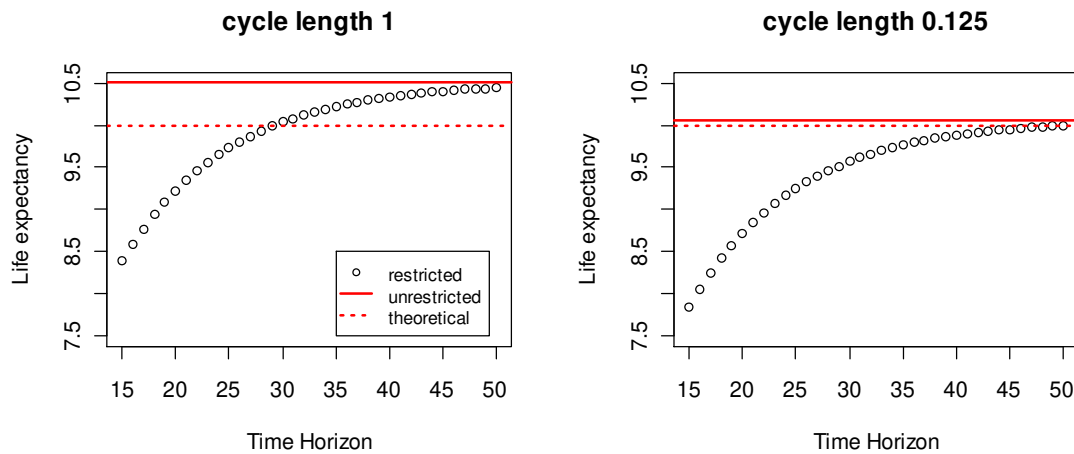
Cycle length	<i>Discrete time unrestricted</i>			<i>Discrete time restricted (time horizon = 20 years)</i>		
	Estimate	Bias		Cycle length	Estimate	Bias
1	10.51	0.508		1	9.22	-0.78
0.5	10.25	0.252		0.5	8.93	-1.07
0.25	10.13	0.126		0.25	8.79	-1.21
0.125	10.06	0.063		0.125	8.72	-1.28
0.015625	10.01	0.008		0.015625	8.65	-1.35

Unrestricted life expectancy ( $E_1[T]$ ) evaluated through the discretized model is always bigger than or equal to the theoretical life expectancy (10 years) (unrestricted case in Table 1, and Figure 2). Hence the associated bias is always positive. As one shortens the cycle length, the discretized solution approaches the continuous time process solution. Note that using a 1 year cycle length overestimates time until absorption by about 0.5 years.



**Figure 2: Theoretical life expectancy calculated from discretized models assuming distinct cycle lengths. The dotted line represents the expected time to absorption of the original continuous time process.**

When the discrete process is evaluated in a finite time horizon, a “restricted” estimate of the expected outcomes is obtained ( $E_2[T]$ ), (Equation 4). The restricted estimate of life expectancy is always less than or equal to the unrestricted one. Figure 3 shows the life expectancy obtained through the application of distinct restriction points, or time horizons, for cycle lengths of 1 and 0.125.



**Figure 3: Theoretical life expectancy calculated from the discretized model with 1 year (plot on the left) and 0.125 years of cycle length (plot on the right). The full line represents the expected time to absorption of the unrestricted discretized time process and the dotted line the expected time to absorption of the true, continuous time phenomena.**

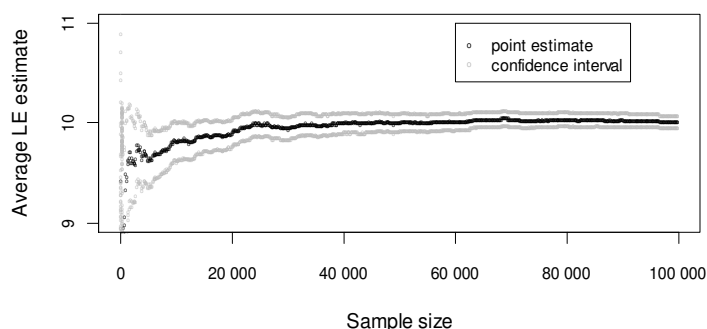
As the time frame of restriction gets larger, the life expectancy approaches the unrestricted one. Hence there is decreasing bias when the time horizon of analysis tends to infinity and the cycle length approaches zero.

Table 2 presents the results of the model when the life expectancy is estimated through Monte Carlo simulation. With 100,000 Monte Carlo simulations, an estimate of 10 years of life expectancy is obtained. The standard error associated with this estimate is 0.032 (Table 2), and the convergence diagnostic plot is shown in Figure 4. Methods based on stochastic simulation are inherently approximate as the simulated sample will never be an exact reproduction of the true distribution.

**Table 2: Life expectancy estimates of a continuous time Markov model evaluated through Monte Carlo simulation.**

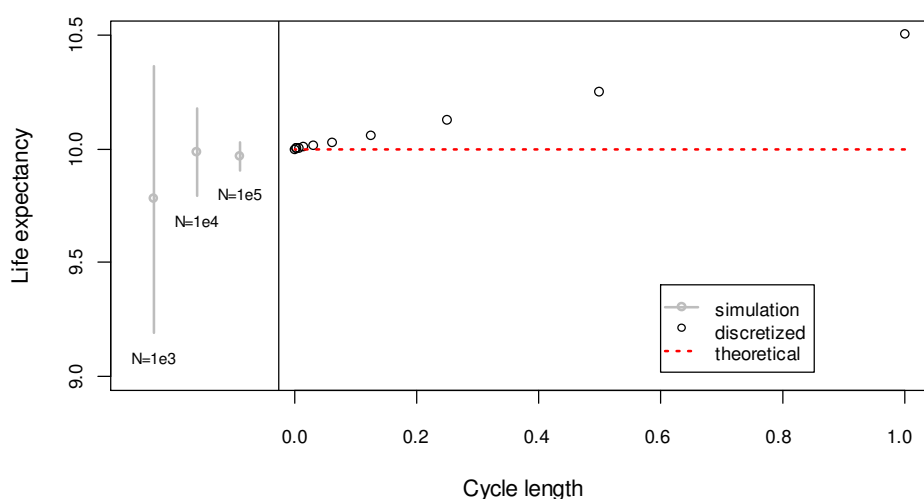
Continuous time		
N simulations	$\hat{E}_3[T]$	$SE(\hat{E}_3[T])$
100	9.85	0.856
1000	9.95	0.318
10000	10.03	0.099
100000	10.00	0.032

Evaluating convergence of the estimates can help the analyst to validate the estimates obtained through Monte Carlo simulation and justify the sample size used (Figure 4). The larger the sample size for the Monte Carlo procedure, the closer is the simulation calculation to the right answer. From the convergence plot, sample sizes less than 20 000 might not be large enough. In addition, presenting the standard error of the expected outcome estimates is important in order to assess the precision of these estimates.



**Figure 4: Convergence diagnostic plot: life expectancy estimates (black) and normal based confidence intervals (grey), obtained through Monte Carlo simulation of a continuous time model considering varying sample sizes (index).**

The time to absorption or life expectancy estimates obtained with both the discretized (unrestricted estimate) and simulation Markov models are represented in Figure 5. The black hollow points represent the unrestricted life expectancy estimates from a discretized process, conditional on distinct values of the cycle length, as seen in Figure 2. The life expectancy estimate obtained through Monte Carlo simulation (for different sample sizes) and the associated 95% confidence interval (normal approximation) is represented in grey.



**Figure 5: Life expectancy estimates obtained through the discretized and continuous time simulation models. Discretized Markov chain results shown in black for distinct cycle lengths (in x axis). The point estimate and confidence intervals for the simulation procedure are depicted in grey for Monte Carlo sample sizes of 1 000, 10 000 and 100 000. The dashed horizontal line represents the theoretical life expectancy.**

The approximations obtained through the unrestricted evaluation of the discretized process are closed form solutions, that is, non-stochastic. Additionally, if one reduces the discretization step (cycle length), the estimates obtained through the discretized process tend to be unbiased. On the contrary, the precision of the Monte Carlo procedure is dependent on the sample size.

### 3.2. Incremental cost, effects, and cost-effectiveness outcomes.

Given that cost-effectiveness estimates are based on an incremental analysis, i.e. additional costs and effects of one intervention over an alternative intervention, a hypothetical alternative treatment option was defined. The existence of a new treatment was assumed to reduce the risk of dying by

20% relative to standard treatment. The use of the new treatment, when displacing the standard one, is expected to bring gains of 2.5 years of life expectancy per patient. In addition, it was assumed that patients undergoing treatment with the standard alternative incur £5 000 per year when alive and are assigned a utility weight of 0.8 per year. The new treatment costs an additional £2 250 per year lived, and does not improve patient health related quality of life.

Adopting the new technology over the comparator gives an exact incremental gain in life expectancy of 2.5 years. This equates to 2 additional QALYs gained, but at an additional cost of £40 625 (exact solution). The true expected ICER related to the adoption of the new health technology is therefore £20 312.5 per QALY gained.

Using the discretized model to evaluate the incremental cost, effect and cost-effectiveness outcome returns the results shown in Table 3.

**Table 3: Incremental costs, effectiveness (LE, life expectancy, and QALYs) and cost-effectiveness outcomes estimated through the discretized Markov model, for distinct cycle lengths. Unrestricted and restricted estimates.**

Cycle length	<i>Unrestricted estimates</i>					<i>Restricted estimates (time horizon = 30 years)</i>				
	Incremental outcomes			Cost-effectiveness		Incremental outcomes			Cost-effectiveness	
	LE (years)	QALYs (years)	Costs (£)	ICER (£/QALY)	bias	LE (years)	QALYs (years)	Costs (£)	ICER (£/QALY)	bias
1.0000	2.4983	1.9987	39507	19767	-546	1.8825	1.5060	33977	22561	2248
0.5000	2.4996	1.9997	40064	20035	-277	1.8737	1.4989	34434	22972	2660
0.2500	2.4999	1.9999	40344	20173	-140	1.8689	1.4951	34663	23184	2872
0.1250	2.5000	2.0000	40484	20242	-70	1.8664	1.4931	34778	23292	2979
0.0156	2.5000	2.0000	40607	20304	-9	1.8642	1.4914	34879	23387	3074

Incremental outcomes evaluated through the unrestricted discretized model appear to be less prone to bias than non-incremental estimates, naturally due to their relative nature. QALY gains estimated by a discretized model considering a cycle length of one year are estimated to be 1.9987 when the true expected gains are 2 QALYs, returning an absolute bias of 0.013 QALYs. For the current example, although gains in effectiveness are overestimated when long cycle lengths are considered, both the incremental costs and ICER are underestimated. When restricting the time horizon to 30 years, the ICER is overestimated and reducing the cycle length does not guarantee a better approximation.

Monte Carlo estimates of incremental outcomes are theoretically unbiased when convergence is achieved. With a sample size of only 100 simulations, the estimate of the ICER is as large as £85 179 per QALY with a bias of £64 866. Increasing the number of simulations to 100 000 (using distinct seeds for the random number generator each time a sample size is set), results in a bias as low as £168/QALY (Table 4).

**Table 4: Incremental cost, effectiveness (LE, life expectancy, and QALYs) and cost-effectiveness estimates, obtained from continuous time model through Monte Carlo simulation for varying Monte Carlo sample sizes.**

N simulations	Incremental outcomes, mean (se)			Cost-effectiveness, mean (se)	
	LE (years)	QALYs	Costs (£)	ICER (£/QALY)	bias
100	0.45 (2.653)	0.36 (2.122)	30880 (16534)	85179 (12124)	64866
1000	2.07 (0.702)	1.65 (0.562)	37967 (4391)	22964 (3235)	2651
10000	2.30 (0.224)	1.84 (0.179)	39303 (1400)	21405 (1029)	1092
100000	2.46 (0.071)	1.97 (0.057)	40365 (442)	20481 (325)	168

For 100 000 simulations, the standard error of the ICER estimate is £325/QALY returning a confidence interval based on the normal distribution of £19 844 to £21 118. The Monte Carlo simulation estimates of incremental outcomes, although theoretically unbiased, are surrounded by uncertainty.



## 4. Discussion

In published health technology assessment studies the choice of model design is rarely adequately justified. The current work addresses this issue noting that ideally DAMs should represent phenomena occurring in continuous time. Often, continuous time models do not return a closed form solution (e.g. semi-Markov models) or these solutions are mathematically burdensome to derive (e.g. Markov models with complex structures). In such cases, discretized models are often evaluated but with little regard to the associated bias which is dependent on the cycle length (or discretization step). Alternatively, continuous time models evaluated by Monte Carlo simulation can be used but these simulation methods return imprecise estimates, where their precision is dependent on the dimension of the simulated sample.

We have used an example for which exact solutions are available. The example, even simple, intends to demonstrate how important it is to acknowledge and consider determinants of bias in the estimation. We have shown that, when alternative models can be applied to represent a continuous time phenomena, it is preferable to implement a cohort discretized model than a simulation model, as the bias from the first can be assessed by reducing the cycle length, whilst the second is inherently stochastic. And these recommendations are directly applicable to any other (more complex) situation.

Although discretized cohort models can produce valuable estimates of cost and effectiveness outcomes, the evaluation of cycle length has received little attention when applied in cost-effectiveness assessment. The cycle length is the basis of use of numerical approximations and its importance is recognised in specialized literature.<sup>17</sup> As these cohort models constitute approximate solutions, the definition of cycle length cannot be solely based on data availability or clinical feasibility<sup>25</sup>, but should be varied to examine small changes in outcomes.

In the current work, the use of continuity corrections such as the half-cycle correction was not evaluated. Neither was the use of methods to accelerate convergence in numerical analysis (e.g. Richardson's extrapolation, see <sup>27</sup>) where the necessary accuracy is achieved without needing very short cycle lengths. Although the implementation of these measures is intended to reduce the bias of discretizing the process, the assessment of their effectiveness will always be dependent on reducing the cycle length until no significant changes in the decision are produced.

When designing an economic evaluation study, we argue that the analyst cannot ignore the use of discretized cohort models unless all the conventionally defined models are deemed inappropriate to represent the decision problem context. In this case, simulation modelling should be considered as its use will be translated into gains in accuracy.<sup>28</sup>

Simulation models benefit from the lack of structural restrictions. This characteristic accounts for the flexibility of such models, but it is the main reason for the lack of transparency attributed to simulation models.<sup>29</sup> While cohort models represent a well defined relation between parameters and listing the input estimates can be enough to replicate the analysis, simulation models can often only be reproduced when the programmed code is made available. Frequently in the health technology assessment literature simulation models are reported incompletely, their use is not adequately justified, and these are often set up with structural features trivial to the appraisal. The use, design and reporting of simulation models could be greatly improved if more guidance is made available. To overcome the difficulty of conducting PSA alongside simulation models, efficient programming<sup>30</sup> and emulators<sup>31,32</sup> must be further explored. Also, it is important to evaluate convergence and precision of the model estimates, and these could be used to define the Monte Carlo sample size and increase efficiency.

The evaluation conducted showed that the incremental outcomes, which are the focus of economic evaluation of health technologies, are less prone to bias due to their relative nature. Nevertheless, the absolute bias will be dependent on the design and structure of the model and 'real life' examples may return less accurate results, e.g. models designed to represent the movement through a sequence of states, or models considering time-depend transitions.

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## Appendix

### Specification of a homogeneous discrete time Markov model

Consider a discrete time Markov chain, where  $\{X_{t_n}\}_{n=\{1,2,\dots\}}$  represents the sequence of states the process occupies. By evaluating time in a discrete way, the parameter space is finite or countably infinite. The state space  $E$  is identical to the one defined in the continuous time process and comprehends a finite set of mutually exclusive disease states.

Discrete time Markov processes are completely defined by the transition function and by the probability distribution at the start of the first cycle  $t_0 = 0$ ,  $\boldsymbol{\pi}^{(0)}$ . The vector  $\boldsymbol{\pi}^{(0)} = \{\pi_i^{(0)} : i \in E\}$  describes the probability of the process starting in each of the set of states defined.

The one step transition function,  $P_{ij}^{t_n}$ , can be formally defined as

$$P_{ij}^{t_n} = P[X_{t_{n+1}} = j | X_{t_n} = i], \quad (6)$$

and represents the probability of the process being in state  $j \in E$  at time  $t_{n+1}$ , knowing that at  $t_n$  the process is in state  $i \in E$ . As transition probabilities are stationary and assuming a constant cycle length,  $l = t_{n+1} - t_n$ , for all  $n$ , a single transition matrix (one-step) can be established and its notation simplified to  $\mathbf{P} = \{P_{ij} : i, j \in E\}$ . In a homogeneous process, the unconditional probability of being in each of the different states,  $\boldsymbol{\pi}^{(n)}$ , after the  $n$ th transition, is defined as

$$\boldsymbol{\pi}^{(n)} = \{\pi_i^{(n)} = P[X_{t_n} = i], i \in E\} = \mathbf{P}^n \cdot \boldsymbol{\pi}^{(0)}. \quad (7)$$

In discrete time homogeneous Markov models,  $E[T]$  can be calculated through the following system of equations:

$$w_i = 1 + \sum_j P_{ij} w_j, \quad (8)$$

where  $w_i$  is the expected number of steps before entering an absorbing state given that the process starts in the  $i$ th state.

### Monte Carlo simulation procedures

In the general case, if one represents the relationship between input parameters,  $\mathbf{X}$ , and outputs,  $Y$ , as a function  $g(\mathbf{X})$ , then the simulation of occurrences of  $\mathbf{X}$  can be used to express  $Y$ ,  $Y = g(\mathbf{X})$ . The estimation of the quantity of interest  $E_Y[Y]$  can be achieved through the empirical mean of  $g(\mathbf{x}_i) : i = \{1, \dots, N\}$ ,  $\frac{1}{N} \sum_{i=1}^N g(\mathbf{x}_i)$ , where  $\mathbf{x}_i$  represent each of the  $N$  independent realizations of  $\mathbf{X}$ .

For the example depicted in Figure 1, the outcome time to death,  $T$ , is itself sampled and each of the realizations  $t_i$  contributes to the estimate through an identity function:

$$\hat{E}_3[T] = \frac{1}{N} \sum_{i=1}^N t_i. \quad (9)$$

For the general case, the precision of this approximation can be evaluated through the standard error (estimated) of the Monte Carlo procedure:

$$\frac{1}{\sqrt{N(N-1)}} \left\{ \sum_{i=1}^N \left[ g(\mathbf{x}_i) - \frac{1}{N} \sum_{i=1}^N g(\mathbf{x}_i) \right]^2 \right\}^{1/2}. \quad (10)$$